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Pathology of Paraganglioma and Pheochromocytoma: Review of Articles and Updates in Pathology

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1. Abstract

Paraganglioma is the generic term applied to nonepithelial tumors of paraganglion cells regardless of location. The only exception is the paraganglioma of the adrenal medulla, which is universally known as pheochromocytoma [1].

2. Background and Cell or Origin

Paraganglion cells (paraganglia) are neural crest-derived cells closely associated with the autonomic nervous system, and divided into adrenal (i.e., the adrenal medulla) and extra-adrenal categories [2].

Extra adrenal paraganglia are predominantly associated with the sympathetic nervous system in the thorax, abdomen and pelvis (bilateral paravertebral along the sympathetic chain) and the parasympathetic nervous system in the head and neck area. The adrenal medulla is predominantly associated with sympathetic nervous system [2].

Parasympathetic paraganglia are closely associated with the vagus and glossopharyngeal nerves. Among the parasympathetic paraganglia are Carotid bodies and Aortic bodies that serves as chemoreceptors and baroreceptors detecting the changes in arterial partial pressure of oxygen (PO2), PH and blood pressure.

Organ of Zuckerkandl is term applied to the collection of paraganglion cells that are located near the bifurcation of the abdominal aorta. These group of cells are predominantly associated with the sympathetic nervous system. These cells are more prominent in the fetal life until early childhood (3-5 years of age) but undergo regression by the age of 14 [3].

Paraganglion cells are also present in the visceral organs (e.g., bladder wall) and can arise to paragangliomas.

Paraganglion cells are also known as chromaffin cells, although the two terms are not identical. The terms chromaffin shows affinity to chromium salt. These cells are stained yellow/brown upon treating with chromium salt due to the presence of catecholamine metabolites. It is important to know that the parasympathetic paraganglia are predominantly “non-chromaffin” cells due to the absence of the catecholamine metabolites [4].

3. Epidemiology

Paragangliomas/pheochromocytomas are uncommon tumors and various studies show the incidence between 2 and 8 per million, with a prevalence between 1:2500 and 1:6500. The annual incidence in the USA is approximately 500-1600 cases per year. Past studies have reported the prevalence of paragangliomas/pheochromocytomas to range from 0.2% to 0.6% in hypertensive patients [5].

A more recent study from Korea showed that the paragangliomas and pheochromocytomas have the prevalence of 2.13 per 100,000 persons and an age-standardized incidence of 0.18 per 100,000 person-years [6].

A nationwide study from Netherland shows the overall age-standardized incidence rates of pheochromocytoma 0.46 (95% CI:0.39–0.53) per 100,000 person-years from 2011–2015. For paragangliomas the overall age-standardized incidence rates were

0.11 (95% CI: 0.09–0.13) per 100,000 person-years, respectively. The same study mentioned that the incidence of the disease has increased in the last decade compared to prior.

Paragangliomas/pheochromocytomas peak between the 3rd and 5th decades of life, and approximately 20% of cases are in pediatric patient5. Our data from the patients with head and neck paragangliomas show the mean age of presentation was 54 years old [7].

There are various reports in the literature regarding the male to female ratio. Some studies reported no significant difference in prevalence between the sexes, while findings from another study demonstrated a slight female preponderance [6, 8].

Some studies reported the male-to-female ratio to be approximately equal among patients with hereditary paraganglioma, while sporadic tumors are more common in women than men [9].

However, majority of the researchers agree that head and neck paragangliomas are more common among the females [10, 11]. Our data of the head and neck paragangliomas also showed a female to male ratio of 3.8:1 [7].

4. Locations

Paragangliomas have been found in practically every site in which normal paraganglia are known to be present. Pheochromocytomas are limited to the adrenal medulla but accounts for 85% of all the paraganglioma/ pheochromocytomas.

Ten percent of the remaining tumors are extra adrenal sympathetic paragangliomas. Approximately, 75% of the sympathetic paragangliomas are present in the abdominal area with a higher predilection in the perinephric and periaortic areas (associated with Organ of Zuckerkandl). Pelvic paragangliomas are predominantly in the bladder region and can involve the bladder wall [12].

Head and neck parasympathetic paragangliomas are the least common tumor type and majority of them involves the carotid body, middle ear area (jugulotympanic paragangliomas), base of the skull region (jugular foramen) and along the glossopharyngeal and vagal nerves [13].

Our data showed that approximately 50% of the head and neck paragangliomas involve the carotid body [7].

5. Clinical Presentation

The majority of pheochromocytomas and sympathetic paragangliomas present with sign and symptoms of excess catecholamine release and include headaches, palpitations, profuse sweating, anxiety, panic attacks and paroxysmal hypertension [14]. In contrast, parasympathetic paragangliomas are non-secretory and present with neck mass or mass effects including tinnitus, hearing loss or deafness [14].

6. Morphology and Histopathology

Paragangliomas and pheochromocytomas are highly vascular tumors. These tumors are morphologically and microscopically indistinguishable regardless of their locations. Grossly, the tumors are relatively well-defined masses with pseudo capsules and yellow-tan-brown cut surfaces and variable degree of hemorrhage (Figure 1A-B).

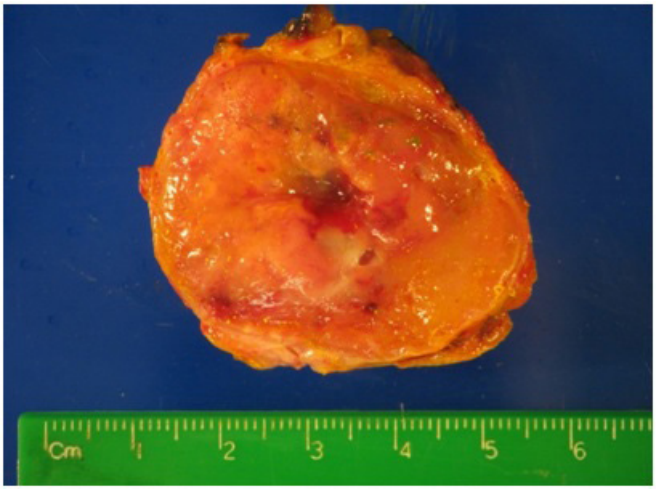


Figure 1A: Pheochromocytoma shows a rubbery, firm, tan, brown-yellow cut surface with areas of hemorrhage, a pseudo capsule, and a central scar.

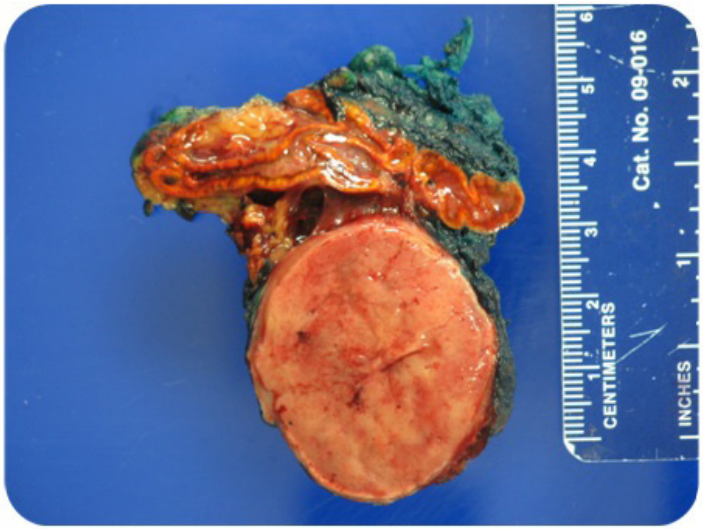


Figure 1B: Extra adrenal paraganglioma: Well defined mass with tan-brown cut surface and variable degrees of hemorrhage. The attached adrenal gland is not involved.

Microscopically these tumors are composed of two cell types: The Chief cells and the sustentacular cells. The chief cells are the neuroendocrine cells and are large round to oval cells with abundant granular basophilic cytoplasm in a nesting (zellballen) or trabecular pattern of cells within a prominent vascular network. The sustentacular cells are inconspicuous spindle cells surrounding the nests of the chief cells (Figure 2A-D).

Similar to endocrine tumors, there might be variable degree of cytologic atypia, necrosis, mitotic activity and infiltrative growth and these features are not predictors of malignancy [7].

By immunohistochemistry, chief cells are positive for NSE, chro-

mogranin, synaptophysin, neurofilaments, GATA 3, PHOX2B, opioid peptides, serotonin, somatostatin, various other peptide hormones and tyrosine hydroxylase (can be negative in parasympathetic paragangliomas) and are negative for s-100 and cytokeratins. Sustentacular cells are positive for s-100 and negative for neuroendocrine markers [1, 15] (Figure 3A-D).

Keratin negativity is integral for paragangliomas/pheochromocytomas and keratin positive tumors with similar morphology should be categorize as neuroendocrine tumors. Ki-67 proliferation index is variable but is usually low.

By electron microscopy, chief cells have abundant cytoplasmic neurosecretory granules and may have giant mitochondria with para crystalline inclusions. Sustentacular cells wrap around chief cells and lack neurosecretory granules [16].

Sclerosing paraganglioma is a morphologic variant of paraganglioma with scattered tumor cells in a background of abundant sclerosis. It poses a diagnostic challenge to the pathologists. Our data on head and neck paragangliomas showed that 40% (2 of 5 cases) of the sclerosing paragangliomas showed metastasis to the adjacent lymph nodes (Figure 4). However, none of them showed distant metastasis. Sclerosing paragangliomas may have more aggressive histological behavior [7].

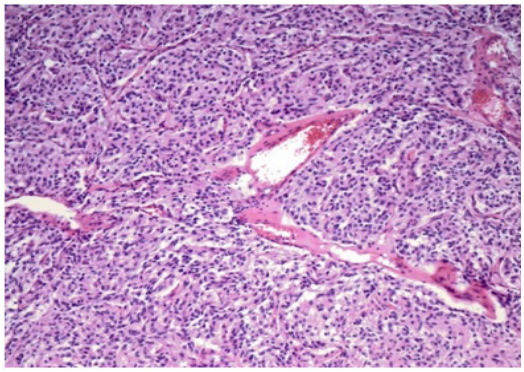


Figure 2-A1: Medium power view of paraganglioma. The tumor is a highly vascular tumor and composed of round to oval chief cells with abundant basophilic granular cytoplasm supported by inconspicuous spindle sustentacular cells. This image shows no cytologic atypia, mitosis or necrosis.

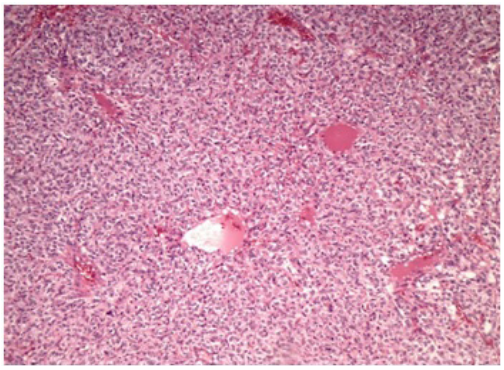


Figure 2-A2: medium power view of paraganglioma. The tumor is more cellular, highly vascular tumor and composed of round to oval chief cells with abundant basophilic granular cytoplasm supported by inconspicuous spindle sustentacular cells. This image shows no cytologic atypia, mitosis or necrosis.

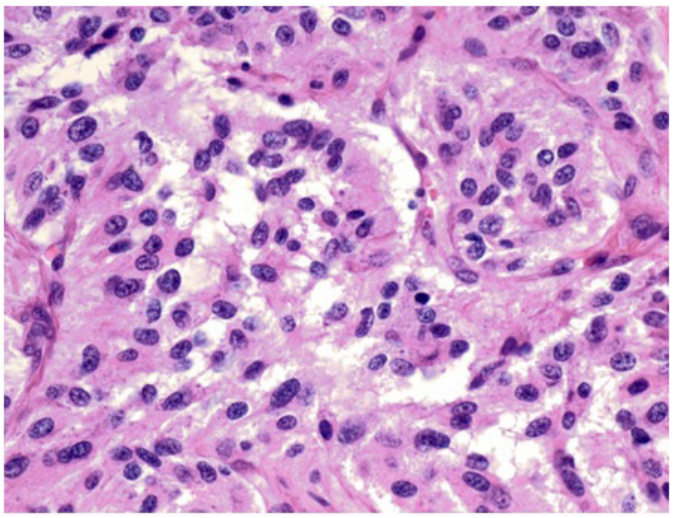


Figure 2-B1: High power image of paraganglioma showing oval chief cells with abundant granular cytoplasm with zellballen pattern, surrounded by spindle sustentacular cells.

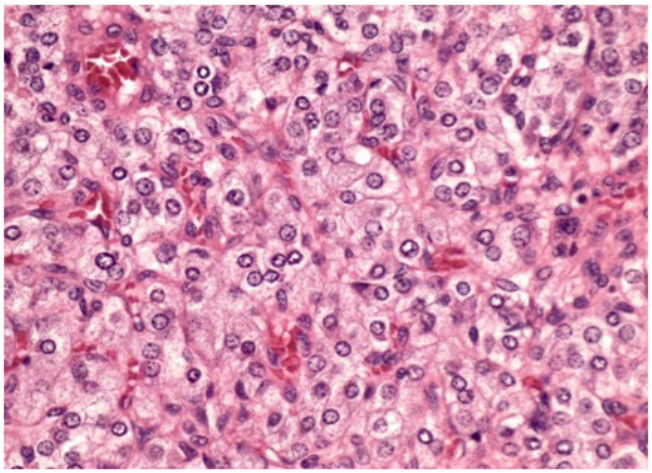


Figure 2-B2: High power image of paraganglioma showing oval chief cells with abundant granular cytoplasm with zellballen pattern, surrounded by spindle sustentacular cells.

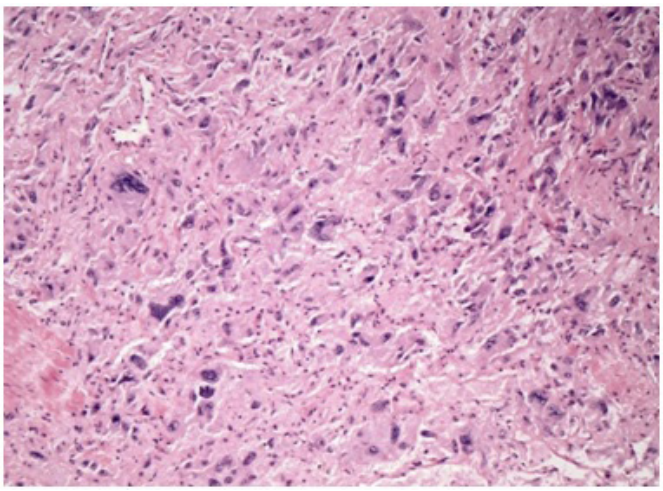


Figure 2C: This paraganglioma shows marked cytologic atypia. Cytologic atypia is not a predictor of malignant behavior in paragangliomas/pheochromocytomas

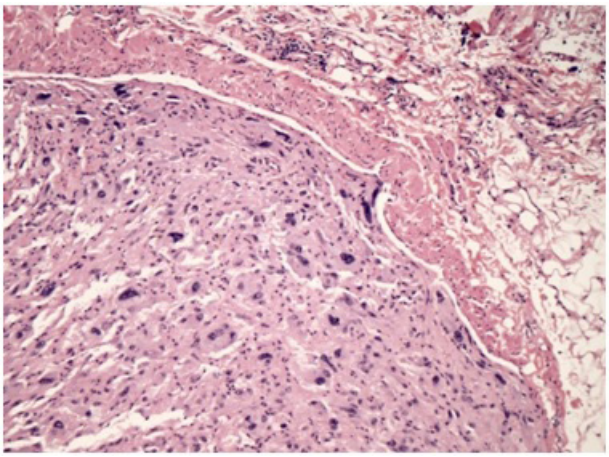
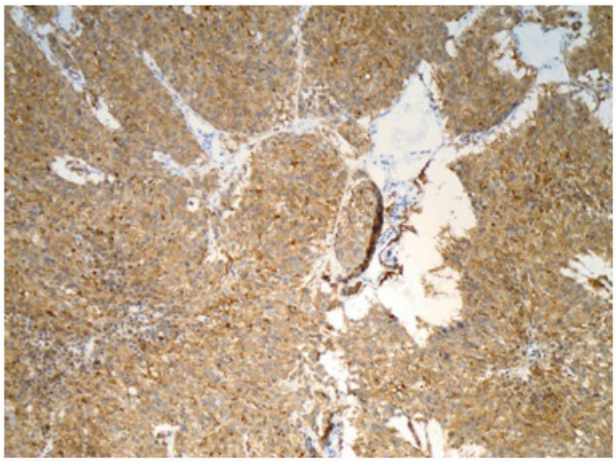


Figure 2D: vascular invasion by paraganglioma. Vascular invasion is not a predictor of malignant potential by paraganglioma/pheochromocytoma.



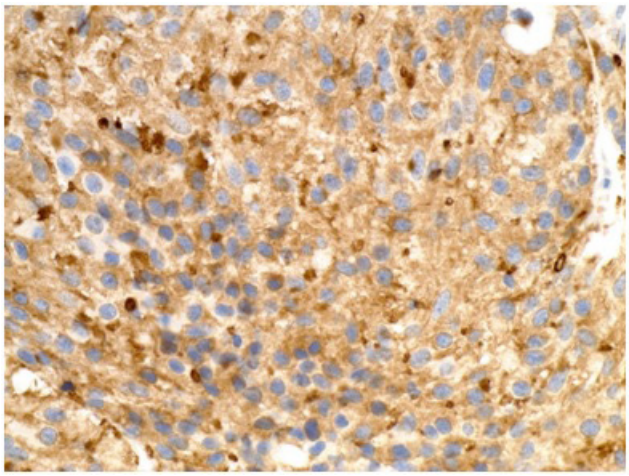


Figure 3A-B: Low and high-power images of paraganglioma with positive synaptophysin immunostain.

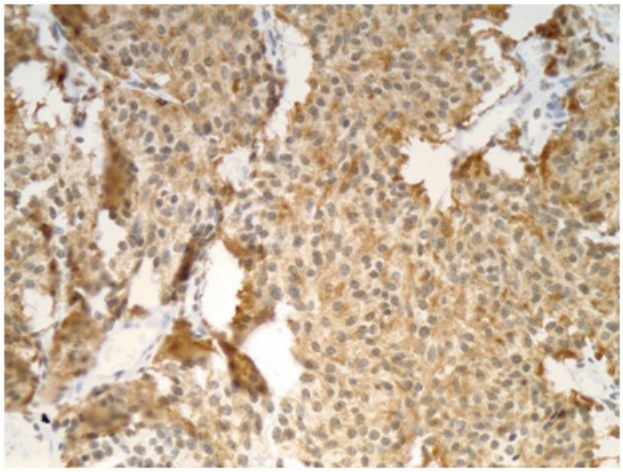


Figure 3C: Medium power images of paraganglioma with positive chromogranin immunostain.

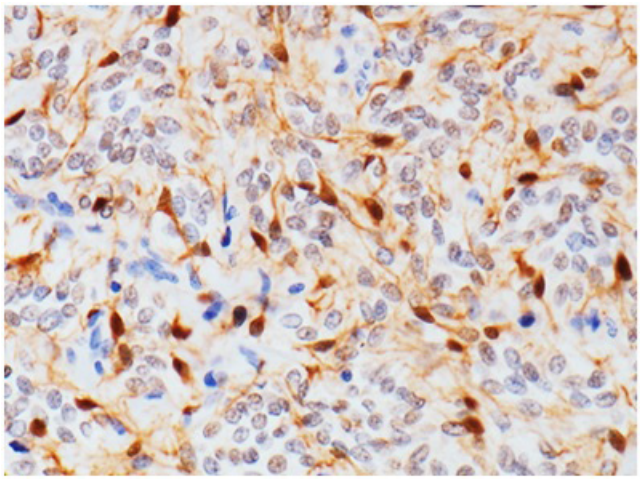


Figure 3D: S100 immunostain highlights the spindle sustantacular cells in paraganglioma

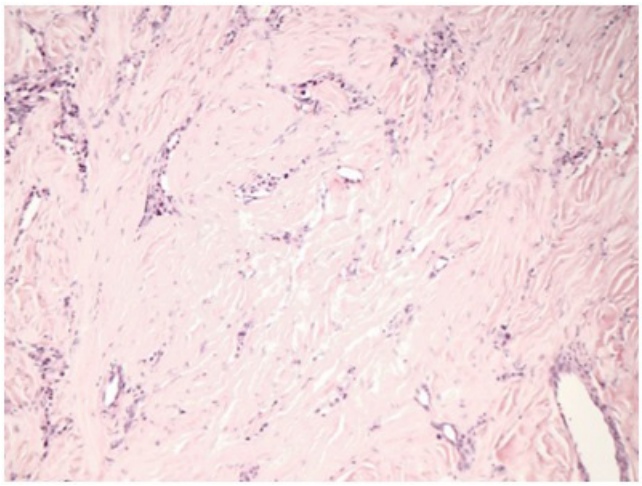


Figure 4: Sclerosing paraganglioma: clusters of tumor cells in a background of extensive sclerosis

7. Malignant Paraganglioma/Pheochromocytoma and Pathologic Staging

The only reliable factor in determining a malignant nature of a paraganglioma/pheochromocytoma is if the tumor metastasize. Although microscopic features or clinical manifestation are not a reliable predictor of malignancy, tumors with certain genetic mutations including SDHB mutations are more likely to metastasize. The most common locations of metastases are the lymph nodes (80%), skeleton (72%), liver (50%), and lungs (50%) [17]. Metastatic disease seen in 5-20% of pheochromocytomas and in 15-35% of sympathetic paragangliomas [18].

Multiple prior attempts in associating microscopic findings with malignancy potential resulted in a "PASS score" which incorporated cellular atypia, capsular invasion, vascular invasion, mitosis and ki-67. A PASS score <4 or ≥ 4 could suggest benign versus malignant lesion respectively [19].

Although worrisome histologic features are worth to mention in the report, they should not be used perse to diagnose malignancy in the absence of metastatic disease. More recently, SDHB protein loss by immunohistochemistry was shown to add additional prognostic information by predicting for higher risk of metastatic disease [1].

American Joint Committee on Cancer (AJCC) 2017, 8th edition classified paragangliomas and pheochromocytomas based on T (tumor size), N (lymph node metastasis) M (distant metastasis). In concordance with the prior studies that showed unreliable correlation between the microscopic features and malignant potential of paraganglioma/pheochromocytomas, the AJCC does not recommend grading these tumors [17].

There are several important caveats that the pathologists should take into consideration: first caveat is parasympathetic (head and neck) paragangliomas are not staged since they are largely benign. Sympathetic paragangliomas of any size are considered T2. The cut off for pheochromocytomas is 5 cm (<5 cm = T1, >= 5 cm= T2).

AJCC also paid special attention to the location of metastatic foci and subclassified the M1 category to M1a (bone), M1b (Lung/Liver or distant Lymph node) and M1c (bone and other sites) due to difference in the survival of the patients with metastatic diseases to various sites. Bone metastases have a better prognosis compared to visceral metastatic lesions. (12 years skeletal vs. 5 years' lung vs. 7.5 years' liver metastases, respectively; log-rank test p value = 0.005) (Figure 5A-C) [17].

Adjacent lymph node metastasis at least in the head and neck paragangliomas, is not necessarily predictor of the distant metastasis and the tumors with metastatic lesions limited to the adjacent lymph nodes have a more indolent behavior (Figure 6A-C) [7].

A very important caveat in identifying a metastatic lesion is considering the possibility of multicentric disease especially in patients with high-risk genetic mutations/syndromes.

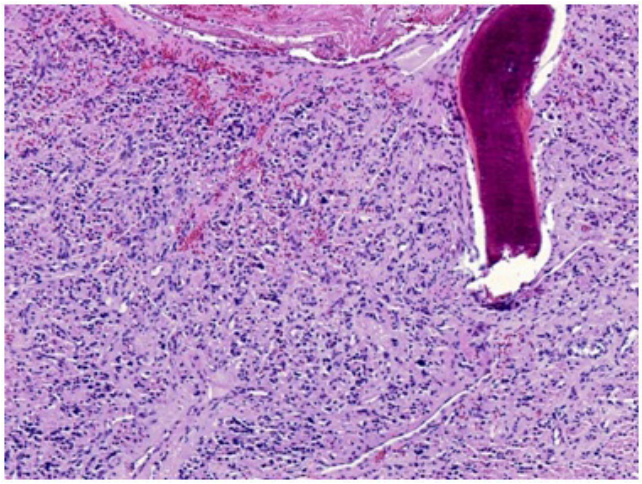


Figure 5A: metastatic paraganglioma to the bone. In this case the tumor cells also show nuclear pleomorphism.

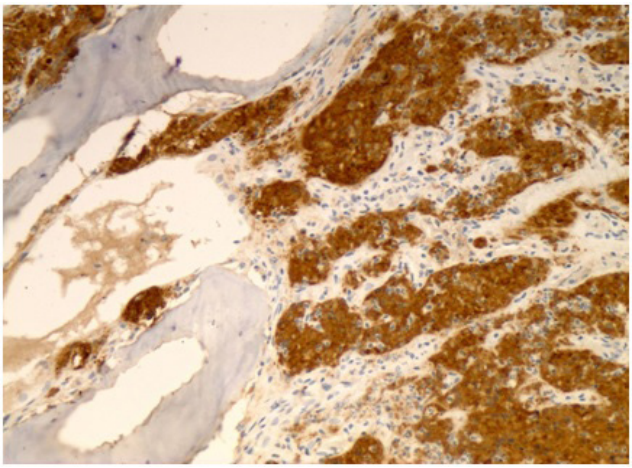


Figure 5B: Synaptophysin immunostain highlights the metastatic paraganglioma

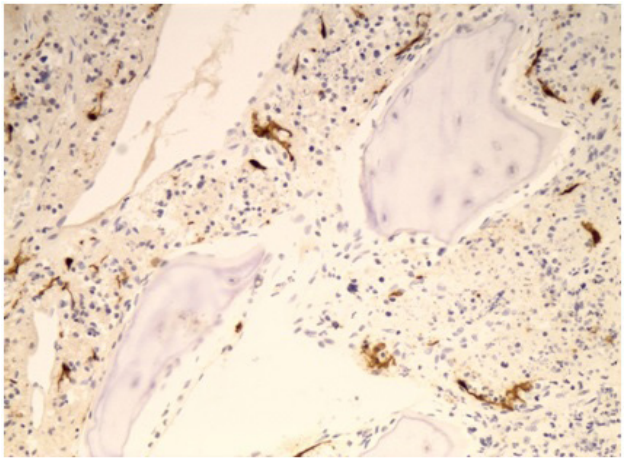


Figure 5C: S100 immunostain highlights the sustentacular cells in the metastatic paraganglioma

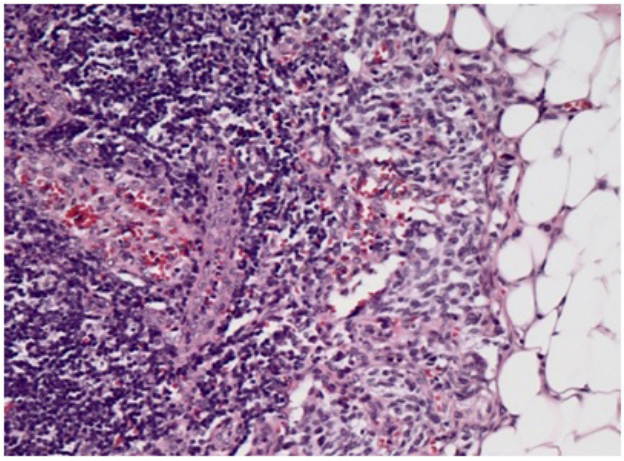


Figure 6A: metastatic paraganglioma to the lymph node

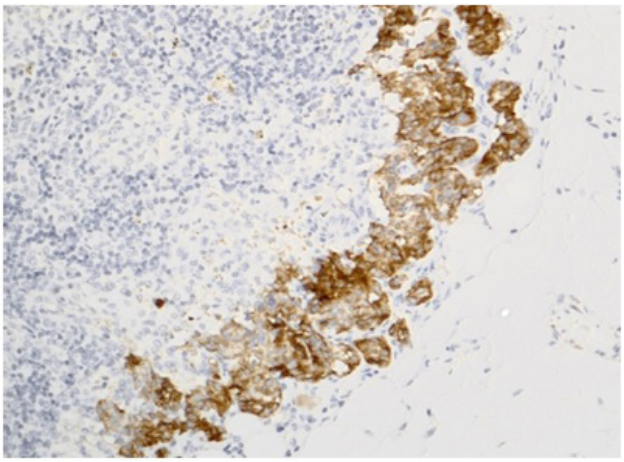


Figure 6B: Synaptophysin immunostain highlights the metastatic tumor cells.

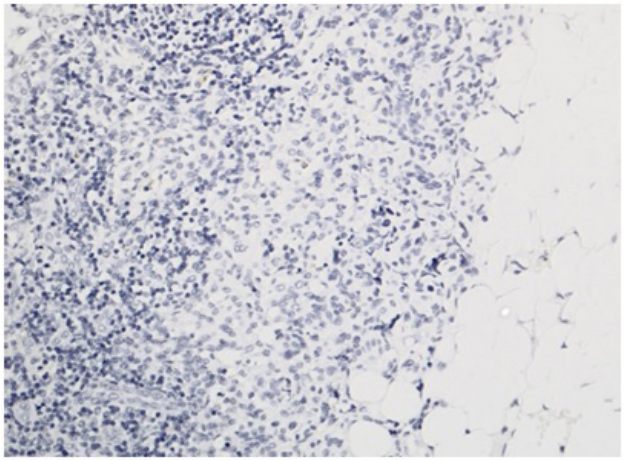


Figure 6C: Metastatic paraganglioma cells are negative for CK AE1/AE3

8. Genetic Features and Associated Syndromes

Germline mutations in predisposition genes are now found in 25–30% of paraganglioma/pheochromocytomas overall [20].

RET was the first gene that was identified to be associated with increased risk of paraganglioma/pheochromocytomas and 10 syndromes could show paraganglioma/pheochromocytomas as part of their manifestation. Among the clinically relevant syndromes are multiple neuroendocrine tumor-2 (MEN-2) due to germline mutations in RET protooncogene (1-5%), Von Hippel–Lindau syndrome due to germline mutations in VHL tumor suppressor gene (4-10%) and germline neurofibromatosis-1 due to mutations in NF-1 tumor suppressor gene (1-5%).

Germline mutations in SDHx genes (paraganglioma syndromes 1-5) due to mutations in succinate dehydrogenase genes SDHA, SDHB, SDHC, SDHD, SDHAF2 are the commonest genetic cause of paraganglioma/pheochromocytomas, occurring in up to 25% cases. All germline mutations of SDHx syndromes are transmitted in an autosomal dominant pattern [14, 20, 21].

The proportion of SDHx mutations among metastatic tumors is the highest among all hereditary paraganglioma/pheochromocytomas, being estimated at 43% to 71% in adults and 70% to 82% in pediatric patients [18, 21].

There are three main molecular pathways that underlie development of these tumors: Theses pathways are hypoxic pathway, Kinase signaling pathway and Wnt signaling pathway [18].

The most notable genes involving in the hypoxic pathway are somatic and germline mutations in Von Hipplel Lindau (VHL) and SDHx. They exhibit a pseudo-hypoxic phenotype, with activity of hypoxia-inducible transcription factors (HIF).

The SDHx Group of genes encode the subunits of succinate dehydrogenase (SDH), which assemble into mitochondrial complex II, in the Krebs cycle and in electron transport via mitochondrial respiratory chain. SDH consists of five proteins: SDHA, SDHB, SDHC, SDHD and SDHAF2. Germline mutation in these five genes have results in activation of hypoxic signaling and epigenetic modifications.

The main players of the kinas signaling pathway are germline or somatic mutations in NF-1 and RET (RAS/RAF/ERK and PI3K-AKT-mTOR), MAX (MYC-associated factor X), TMEM127 (Transmembrane protein 127) and HRAS.

NF-1(17q11.2): Down regulates RAS protein and a downstream RAS-RAF-MAPK signaling cascade. Paraganglioma/pheochromocytomas are rare in patients with neurofibromatosis type 1. RET (10q11.2) can be activated by gain of function mutations in cases of MEN-2 or in some sporadic cases [21].

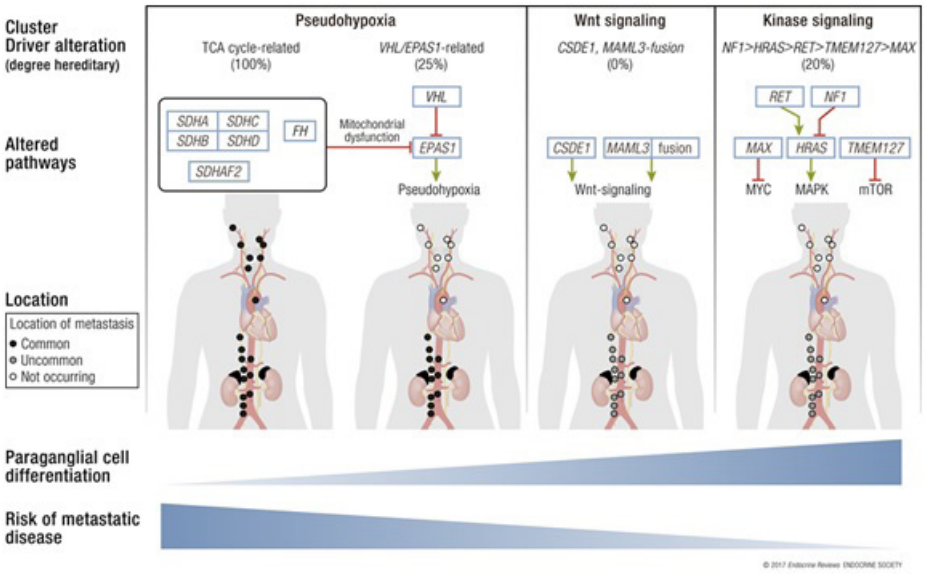


Figure 7: Figure from Crona J, Taïeb D, Pacak K. New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. Endocrine Reviews. 2017;38(6):489-515 18

Different PPGL molecular subgroups with corresponding driver mutations and a proportion of hereditary disease in the respective cluster. TCA cycle–related mutations include SDHA, SDHB, SDHC, SDHD, SDHAF2, and FH genes. MYC, c-MYC induced pathways; MAPK, mitogen-activated protein kinase cascade; mTOR, the mammalian target of rapamycin pathway. Anatomic figure was adopted and modified from Lips et al [24].

The autosomal dominant Carney–Stratakis syndrome is characterized by the association of pheochromocytoma, paraganglioma, or both with gastrointestinal stromal tumors (GISTs), and the so-called 3PAs syndrome (pheochromocytoma, paraganglioma, and pituitary adenoma) is associated with SDHx mutations [14].

Wnt signaling pathway group include somatic mutations in CSDE1 (Cold shock domain containing E1) as well as somatic gene fusions affecting MAML3 (Mastermind like transcriptional coactivator 3) [18].

There are phenotypes/genotype correlation between each susceptibility gene and location of paraganglioma/pheochromocytomas. Mutations in NF1, VHL, and RET usually cause adrenal base pheochromocytomas, with rare paragangliomas reported in some cases. Mutations in SDHC, SDHD, and SDHAF2 lead to head and neck paragangliomas. Mutations in SDHB lead to extra adrenal paragangliomas and increase the risk of malignancy from 31% to 71%. A mutation in this gene is a biomarker of malignancy and a poor prognosis (figure 7) [18, 22]. Multiple primary tumors often occur in patients with germline mutations in RET, VHL, SDHD, or MAX mutations [14].

Different mutations are associated with different patterns of catecholamine production. It is important to know that epinephrin can only be secreted by adrenal medulla and therefor by the pheochromocytomas. Sympathetic paragangliomas outside the adrenal gland are not producing epinephrin.

NF-1-associated pheochromocytomas produce normetanephrine, metanephrine, norepinephrine and epinephrin. Pheochromocytomas with RET mutations often have high levels of epinephrine and metanephrine. VHL associated pheochromocytomas have elevation of both normetanephrine and norepinephrine.

SDHB-associated tumors have and normetanephrine and dopamine predominance. Tumors with SDHC, SDH D, and SDHAF2 are often not secretory (Parasympathetic ganglia in head and neck). In patient with head and neck paraganglioma and high level of catecholamine the presence of another primary tumor in the abdomen or pelvis should be considered [23].

9. Acknowledgement

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